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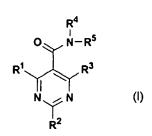
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(54) Title: 2,4-DISUBSTITUTED PYRIMIDINE-5-CARBOXAMIDE DERIVATIVES AS KCNQ POTASSIUM CHANNEL MODULATORS



(57) Abstract: There is provided a method of treatment for disorders responsive to the modulation of KCNQ potassium channels by administering to a mammal in need thereof a therapeutically effective amount of a 2,4-disubstituted pyrimidine-5-carboxamide derivative of Formula (I) wherein R¹, R², R³, R⁴ and R⁵ are as defined in the description. The present invention also provides pharmaceutical compositions comprising openers or activators of the KCNQ potassium channels and especially to the method of treatment of disorders sensitive to KCNQ potassium channel opening activity such as migraine.

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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols) IPC $\frac{7}{600}$ A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, MEDLINE, EMBASE

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Х	US 5 852 028 A (M. J. SUTO ET AL) 22 December 1998 (1998-12-22) cited in the application claims 1-39	5,6
X	US 5 935 966 A (M. J. SUTO ET AL) 10 August 1999 (1999-08-10) cited in the application claims 1-23	5,6
X	US 5 811 428 A (M. J. SUTO ET AL) 22 September 1998 (1998-09-22) cited in the application claims 1-27/	5,6

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Date of the actual completion of the international search 14 June 2002	Date of mailing of the international search report 03/07/2002
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Siatou, E

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Category °	ation) DOCUMENTS CONSIDERED TO BE RELEVANT Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	"ION CHANNELS - MOLECULAR DIVINING RODS HIT THEIR CLINICAK MARK" NEW ENGLAND JOURNAL OF MEDICINE, THE, MASSACHUSETTS MEDICAL SOCIETY, WALTHAM, MA, US, vol. 336, no. 22, 29 May 1997 (1997-05-29), pages 1599-1600, XP001030467 ISSN: 0028-4793 the whole document	1-6
А	WANG H-S ET AL: "KCNQ2 AND KCNQ3 POTASSIUM CHANNEL SUBUNITS: MOLECULAR CORRELATES OF THE M-CHANNEL" SCIENCE, AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE, US, vol. 282, 4 December 1998 (1998-12-04), pages 1890-1898, XP002900985 ISSN: 0036-8075 cited in the application the whole document	1-6
A	LERCHE C ET AL: "Molecular cloning and functional expression of KCNQ5, a potassium channel subunit that may contribute to neuronal M-current diversity" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, US, vol. 275, no. 29, 21 July 2000 (2000-07-21), pages 22395-22400, XP002169157 ISSN: 0021-9258 cited in the application abstract	1-6
A .	MAIN M J ET AL: "MODULATION OF KCNQ2/3 POTASSIUM CHANNELS BY THE NOVEL ANTICONVULSANT RETIGABINE" MOLECULAR PHARMACOLOGY, BALTIMORE, MD, US, vol. 58, no. 2, August 2000 (2000-08), pages 253-262, XP000972245 ISSN: 0026-895X cited in the application abstract /	1-6

In Itional Application No PCT/US 02/04305

		PCT/US 02/04305
C.(Continu	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WICKENDEN ALAN D ET AL: "Retigabine, a novel anti-convulsant, enhances activation of KCNQ2/Q3 potassium channels" MOLECULAR PHARMACOLOGY, BALTIMORE, MD, US, vol. 58, no. 3, September 2000 (2000-09), pages 591-600, XP000972243 ISSN: 0026-895X cited in the application abstract	1-6
A		1-6
COMPANY OF THE PARTY OF THE PAR	·	

Information on patent family members

Ir. stional Application No PCT/US 02/04305

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
US 5852028	Α	22-12-1998	AU	726058 B2	26-10-2000
		•	AU	7013096 A	27-03-1997
			CA	2230896 A1	13-03-1997
			JP	11512390 T	26-10-1999
			WO	9709325 A1	13-03-1997
			US	5935966 A	10-08-1999
US 5935966	Α	10-08-1999	US	5852028 A	22-12-1998
			ΑU	6666798 A	18-09-1998
			WO	9838171 A1	03-09-1998
			ΑU	726058 B2	26-10-2000
			AU	7013096 A	27-03-1997
			JP	11512390 T	26-10-1999
			CA	2230896 A1	13-03-1997
			WO	9709325 A1	13-03-1997
			AU	726522 B2	09-11-2000
			ΑU	7163196 A	27-03-1997
			CA	2230894 A1	13-03-1997
			EP	0850228 A1	01-07-1998
			JP	11512399 T	26-10-1999
~~~~~~~			WO	9709315 A1	13-03-1997
US 5811428	Α	22-09-1998	AU	726522 B2	09-11-2000
			AU	7163196 A	27-03-1997
			CA	2230894 A1	13-03-1997
			EP	0850228 A1	01-07-1998
			JP	11512399 T	26-10-1999
			WO	9709315 A1	13-03-1997